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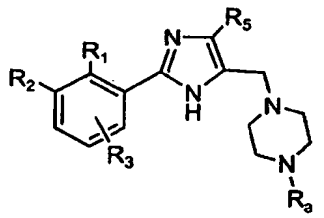
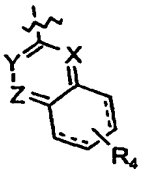


(I)



(II)

(57) Abstract

Disclosed are compounds of formula: (I) or the pharmaceutically acceptable acid addition salts thereof wherein R_a represents (II) where X, Y and Z are the same or different and represent CH or nitrogen; R_1, R_2, R_3 and R_4 independently represent organic or inorganic groups: and R_5 is hydrogen, C_1–C_6 alkyl or halogen, which compounds are useful for the treatment and/or prevention of neuropsychological disorders including, but not limited to, schizophrenia, mania, dementia, depression, anxiety, compulsive behaviour, substance abuse, Parkinson–like motor disorders and motion disorders related to the use of neuroleptic agents.

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2-Aryl-4-(1-[4-heteroaryl]piperazin-1-yl)methylimidazoles: Dopamine D_4 Receptor Subtype Ligands

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to 2-aryl-4-(1-[4-heteroaryl]piperazin-1-yl)methylimidazoles and to pharmaceutical compositions containing such compounds. It also relates to the use of such compounds in the treatment or prevention of psychotic disorders such as schizophrenia and other central nervous system diseases.

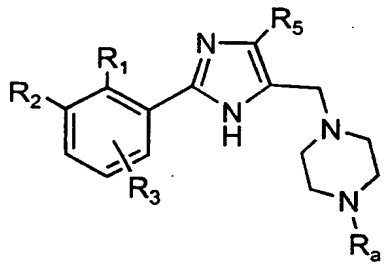
Description of the Related Art

The therapeutic effect of conventional antipsychotics, known as neuroleptics, is generally believed to be exerted through blockade of dopamine receptors. However, neuroleptics are frequently responsible for undesirable extrapyramidal side effects (EPS) and tardive dyskinesias, which are attributed to blockade of D_2 receptors in the striatal region of the brain. The dopamine D_4 receptor subtype has recently been identified (Nature, 350: 610 (Van Tol et al., 1991); Nature, 347: 146 (Sokoloff et al., 1990)). Its unique localization in limbic brain areas and its differential recognition of various antipsychotics indicates that the D_4 receptor plays a major role in the etiology of schizophrenia. Selective D_4 antagonists are considered effective antipsychotics free from the neurological side effects displayed by conventional neuroleptics.

U.S. Patent No. 5,428,164 describes piperidinylmethylphenyl-imidazole derivatives.

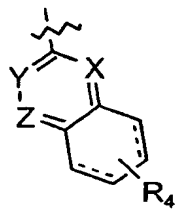
SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with dopamine subtypes. Accordingly, a broad embodiment of the invention is directed to a compound of Formula I:



I

or pharmaceutically acceptable addition salts thereof; wherein:
R_a represents



where X, Y and Z are the same or different and represent CH or nitrogen, provided that at least one of X, Y and Z is nitrogen;

R_1 R_2, R_3 and R_4 independently represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy or SO_2NH_2;

R_5 is hydrogen, C_1-C_6 alkyl or halogen.

Dopamine D_4 receptors are concentrated in the limbic system (Science, 265: 1034 (Taubes, 1994)) which controls cognition and emotion. Therefore, compounds that interact with these receptors are useful in the treatment of cognitive disorders. Such disorders include cognitive deficits which are a significant component of the negative symptoms (social withdrawal and unresponsiveness) of schizophrenia. Other

disorders include those involving memory impairment or attention deficit disorders.

Compounds of the present invention demonstrate high affinity and selectivity in binding to the D_4 receptor subtype. These compounds are therefore useful in treatment of a variety of neuropsychological disorders, such as, for example, schizophrenia, psychotic depression and mania. Other dopamine-mediated diseases such as Parkinsonism and tardive dyskinesias can also be treated directly or indirectly by modulation of D_4 receptors.

Compounds of this invention are also useful in the treatment of depression, memory-impairment or Alzheimer's disease by modulation of D_4 receptors since they exist selectively in areas known to control emotion and cognitive functions.

Thus, in another aspect, the invention provides methods for treatment and/or prevention of neuropsychochological or affective disorders including, for example, schizophrenia, mania, dementia, depression, anxiety, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson-like motor disorders, e.g., Parkinsonism and dystonia, and motion disorders related to the use of neuroleptic agents. In addition, the compounds of the invention are useful in treatment of depression, memory-impairment or Alzheimer's disease. Further, the compounds of the present invention are useful for the treatment of other disorders that respond to dopaminergic blockade, e.g., substance abuse and obsessive compulsive disorder. These compounds are also useful in treating the extrapyramidal side effects associated with the use of conventional neuroleptic agents.

In yet another aspect, the invention provides pharmaceutical compositions comprising compounds of Formula I.

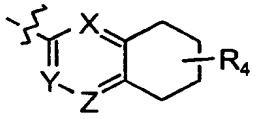
In another aspect, the invention provides intermediates useful in the preparation of compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the invention encompasses 2-aryl-4-(1-[4-heteroaryl]piperazin-1-yl)methylimidazole derivatives of Formula I.

Preferred compounds of Formula I are those where R_1 and R_2 are hydrogen, C_1-C_6 alkyl, halogen, or hydroxy and R_3 is hydrogen. Other preferred compounds of Formula I are those where R_3 is C_1-C_6 alkyl in the 4 position on the phenyl ring. Still other preferred compounds of Formula I are those where R_1 and R_2 represent hydrogen, halgogen, C_1-C_6 alkyl, or hydroxy, provided that one of R_1 and R_2 is hydrogen. Yet other preferred compounds of I are where R_5 is C_1-C_6 alkyl.

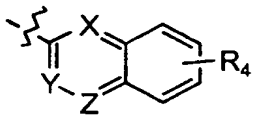
Preferred compounds of Formula I are those where R_a is



Such compounds are referred to hereinafter as compounds of Formula II. In the compounds of Formula II, the definitions of X, Y, Z and R_4 are as set forth above for Formula I.

In preferred compounds of Formula II, X is nitrogen and Y and Z are CH. Such compounds are hereinafter referred to as compounds of Formula IIa. In other preferred compounds of II, X and Y are nitrogen and Z is CH (Formula IIb). In yet other preferred compounds of Formula II, X and Z are nitrogen and Y is CH (Formula IIc).

Other preferred compounds of Formula I are those where R_a is



Such compounds are referred to hereinafter as compounds of Formula III. In the compounds of Formula III, the definitions of X, Y, Z and R_4 are as set forth above for Formula I.

In preferred compounds of Formula III, X is nitrogen and Y and Z are CH (Formula IIIa). In other preferred compounds of III, X and Y are nitrogen and Z is CH (Formula IIIb.). In yet other preferred compounds of Formula III, X and Z are nitrogen and Y is CH (Formula IIIc).

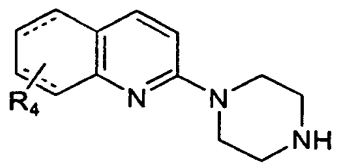
Particularly preferred compounds of Formulas II and III (and of Formulas IIa-c and IIIa-c) are those where R_1 and R_2 are hydrogen, C_1-C_6 alkyl, halogen, or hydroxy and R_3 is hydrogen.

Other particularly preferred compounds of Formulas II and III are those where R_3 is 4-C_1-C_6 alkyl.

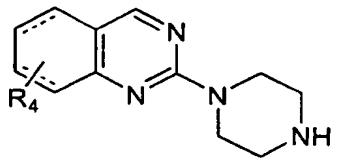
Still other particularly preferred compounds of Formulas II and III are those where R_1 and R_2 represent hydrogen, halgogen, C_1-C_6 alkyl, or hydroxy, provided that one of R_1 and R_2 is hydrogen.

Yet other particularly preferred compounds of Formulas II and III are those where R_5 is C_1-C_6 alkyl.

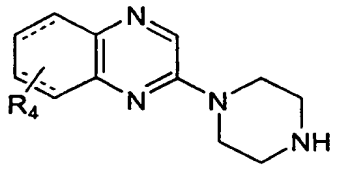
The invention also provides intermediates useful in preparing compounds of Formula I. These intermediates are represented by Formula IVa, IVb, and IVc.



IVa



IVb



IVc

In each of Formulae IVa, IVb, and IVc, R_4 carries the definition set forth above for Formula I.

In certain situations, the compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table 1 and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic,

citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

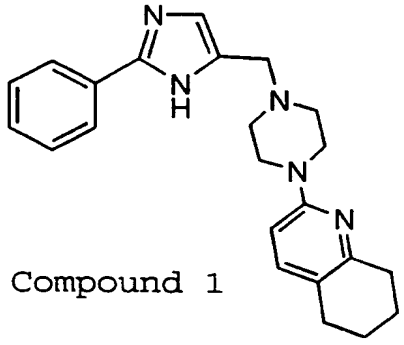
By "C_1-C_6 alkyl" or "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Preferred C_1-C_6 alkyl groups are methyl, ethyl, propyl, butyl, cyclopropyl and cyclopropylmethyl.

By "C_1-C_6 alkoxy" or "lower alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

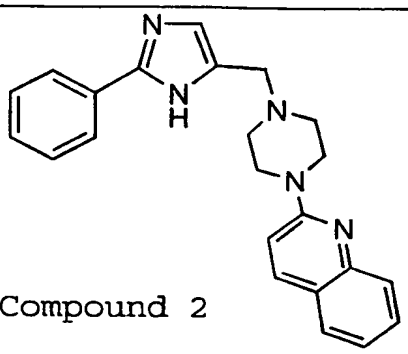
By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

Representative compounds of the invention are shown in Table 1.

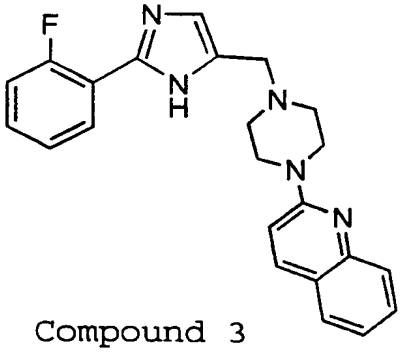
Table 1



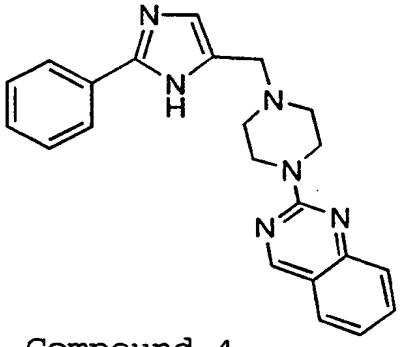
Compound 1



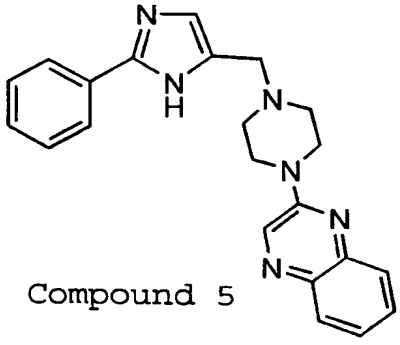
Compound 2



Compound 3



Compound 4



Compound 5

The invention also pertains to the use of compounds of general Formula I in the treatment of neuropsychological disorders. The interaction of compounds of the invention with

dopamine receptors is shown in the examples. This interaction results in the pharmacological activity of these compounds.

The invention also pertains to the use of compounds of general Formula I in the treatment of neuropsychological disorders. The interaction of compounds of the invention with dopamine receptors is shown in the examples. This interaction results in the pharmacological activity of these compounds.

The compounds of general formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general formula I and a pharmaceutically acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of

tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives,

for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or

sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

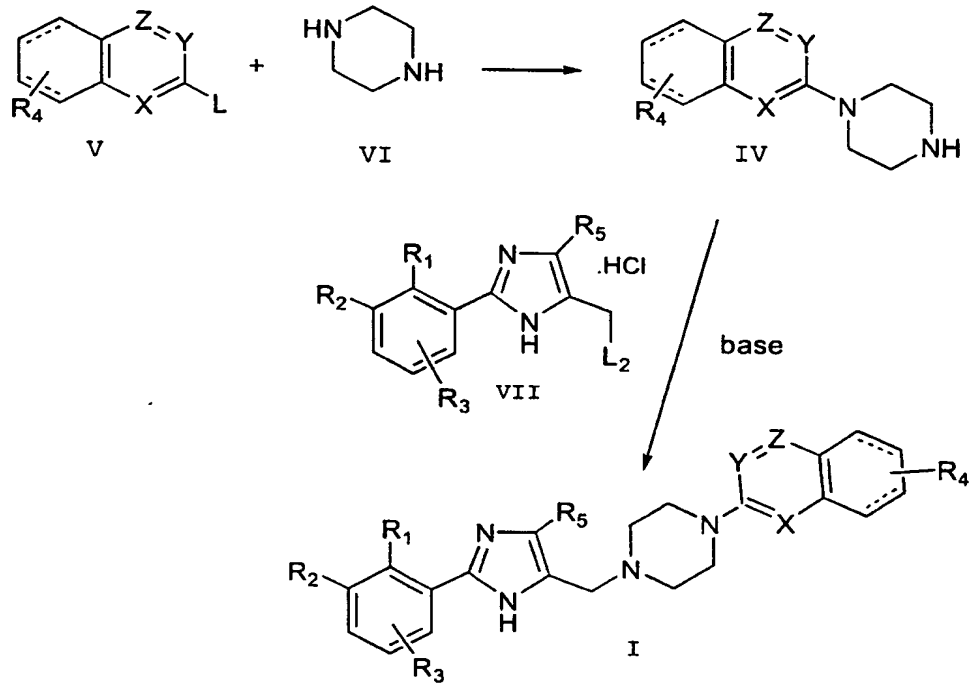
Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to

about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

A representative synthesis of the compounds of the invention is presented in Scheme I. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention.

Scheme I



In Scheme I, the definitions of R_1, R_2, R_3, R_4, R_5, X, Y and Z are as set forth above for Formula 1.

As shown, an azanaphthyl compound of general structure V, carrying an appropriate leaving group L, may be condensed with piperazine (VI) to provide a 1-azanaphthyl piperazine of general structure IV. Compound IV may then be condensed with a imidazole VII having an appropriate leaving group L_2 to provide a compound of Formula 1. The leaving groups L and L_2 may be any suitable leaving group, e.g., a halide, a sulfonate ester, or the like. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

Example 1

Preparation of intermediates

2, 4-Dichloroquinazoline

A solution of 25 g of benzoyleneurea and 12 mL of diethyl aniline in 200 mL of phosphorus oxychloride is refluxed for 4 days. Excess phosphorus oxychloride is removed on a rotovap and the remaining residue poured onto ice. The mixture is extracted with ethyl acetate. The combined organic extracts are washed with water, 1 N NaOH solution, dried and concentrated. The residue is recrystallized from isopropanol to provide 11 g of the dichloroquinazoline as off-white needles (m.p. 118-121 °C.). ^{1}H NMR (DMSO) 8.30 (d, J = 7 Hz, 1H), 8.17

(ddd, J = 7, 7, 1 Hz, 1H), 8.04 (d, J = 7 Hz, 1H), 7.90 (ddd, J = 7, 7, 1 Hz, 1H).

2-Chloroquinazoline

A solution of 2, 4-dichloroquinazoline (5 g) in methylene chloride (100 mL) is combined with 100 mL of saturated brine containing 9% NH_4OH and powdered zinc (5 g). The resultant mixture is refluxed for 4 hours, cooled and filtered through celite. The organic layer is removed, diluted with ethyl acetate (100 ml), washed with 1 N HCl solution, dried and concentrated to yield 2-chloro-quinazoline.

1-Quinazolin-2-ylpiperazine

A solution of 2-chloroquinazoline (5 g) in 20 mL of toluene is added dropwise to a refluxing solution of piperazine (20 g) in 150 mL of toluene. The solution is heated for an additional 24 hours. After cooling to 0 °C for about 30 minutes, the solution is filtered. The filtrate is extracted with 10 % acetic acid. The aqueous extracts are washed with ether, basified and extracted with toluene. The toluene layer is then washed with water, dried and concentrated. The resulting material is placed under vacuum overnight to afford the title compound (6.8 g, m.p. 64-66 °C). ^1H NMR ($CDCl_3$) 9.0 (s, 1H), 7.66 (m, 2H), 7.56 (d, J = 8 Hz, 1H), 7.22 (ddd, J = 8,7,1 Hz, 1H), 4.0 (t, J = 5 Hz, 4H), 3.05 (t, J = 5 Hz, 4H).

Example 2

2-{4-[(2-phenylimidazol-5-yl)methyl]piperazinyl}quinazoline

A sample of 2-phenyl-4-hydroxymethylimidazole (348 mg, 2 mmol) is heated for 5 min in thionyl chloride (5 mL) and subsequently concentrated. Chloroform (10 mL) is added and the solution reconcentrated. The resulting dark oil is then taken up in chloroform (10 mL) and treated with 1-quinazolin-2-ylpiperazine (428 mg, 2 mmol) and triethyl amine (2 mL). After

10 minutes, the reaction is washed with 2 N NaOH solution, dried (Na_2SO_4) and concentrated to provide the title compound (Compound 4) as an oil (640 mg), the hydrochloride salt is prepared in a conventional manner, m.p. 101-105 °C (Compound 4a). ^1H NMR ($CDCl_3$) 9.0 (s, 1H), 7.9 (d, J = 7 Hz, 2H), 7.65 (m, 2H), 7.55 (d, J = 6 Hz, 1H), 7.2-7.4 (m, 4H), 7.0 (s, 1H, imidazole CH), 3.95 (m, 4H), 3.6 (s, 2H), 2.6 (t, J = 5 Hz, 4H).

Example 3

The following compounds are prepared essentially according to the procedures set forth above in Examples 1 and 2.

(a) 2-(4-[{2-Phenylimidazol-5-yl}methyl]piperazin-1-yl)-5,6,7,8-tetrahydroquinazoline (Compound 6).

(b) 2-(4-[{2-(4-Methylphenyl)imidazol-5-yl}methyl]piperazin-1-yl)-5,6,7,8-tetrahydroquinazoline hydrochloride.

(c) 2-(4-[{2-(3-Fluorophenyl)imidazol-5-yl}methyl]piperazin-1-yl)-5,6,7,8-tetrahydroquinazoline hydrochloride.

(d) 2-(4-[{2-Phenyl-5-methylimidazol-5-yl}methyl]piperazin-1-yl)-5,6,7,8-tetrahydroquinazoline dimaleate.

(e) 1-[(2-phenylimidazol-5-yl)methyl]-4-(2-5,6,7,8-tetrahydroquinolyl)piperazine (Compound 1).

(f) (1-[(2-phenylimidazol-5-yl)methyl]-4-(2-5,6,7,8-tetrahydroquinolyl)piperazine hydrobromide. (m.p. 270-275 °C, Compound 1a).

(g) 1-[(2-phenylimidazol-5-yl)methyl]-4-(2-quinolyl)piperazine (Compound 2).

(h) 1-[(2-phenylimidazol-5-yl)methyl]-4-(2-quinolyl)piperazine hydrobromide (m.p. 257-260 °C, Compound 2a).

(i) 2-(4-[{2-Phenylimidazol-5-yl}methyl]piperazin-1-yl)-6-fluoroquinoline hydrobromide (m.p. 199-201 °C).

(j) 1-{[2-(2-fluorophenyl)imidazol-5-yl]methyl}-4-(2-quinolyl)piperazine (Compound 3).

(k) 1-{[2-(2-fluorophenyl)imidazol-5-yl]methyl}-4-(2-quinolyl)piperazine oxalate (m.p. 218-220 °C, Compound 3a).

(l) 2-{4-[(2-phenylimidazol-5-yl)methyl]piperazinyl}quinoxaline (m.p. 96-99 °C, Compound 5).

Example 4

Assays For D_2 And D_4 Receptor Binding Activity

The pharmaceutical utility of compounds of this invention is indicated by the assays for dopamine receptor subtype affinity described below.

Pellets of COS cells containing recombinantly produced D_2 or D_4 receptors from African Green monkey are used for the assays. A sample is homogenized in 100 volumes (w/vol) of 0.05 M Tris HCl buffer at 4° C and pH 7.4 and then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is again centrifuged at 30,000 x g and the final tissue sample is frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05 M Tris HCl buffer containing 100 mM NaCl.

Incubations are carried out at 48°C and contain 0.4 ml of tissue sample, 0.5 nM ^{3}H-YM 09151-2(Nemonapride, cis-5-Chloro-

2-methoxy-4-(methylamino)-N-(2-methyl-2-(phenylmethyl)-3-pyrrolidinyl)benzamide) and the compound of interest in a total incubation of 1.0 ml. Nonspecific binding is defined as that binding found in the presence of 1 mM spiperone; without further additions, nonspecific binding is less than 20% of total binding. The binding characteristics of representative compounds of this invention for the D_2 and D_4 receptor subtypes are shown in Table 2 for rat striatal homogenates.

Table 2

Compound Number	D_4 K_i (nM)	D_2 K_i (nM)
1a	14	>1000
2a	9	784
3a	17	978
4a	3	2676
5	8	2052

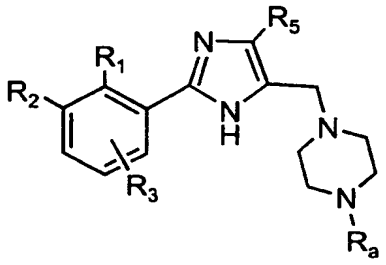
The binding constants of compounds of Formula I for the D_4 receptor, expressed in nM, generally range from about 0.5 nanomolar (nM) to about 100 nanomolar (nM), and preferably less then about 25nM. These compounds typically have binding constants for the D_2 receptor of at least about 500 nM. Thus, the compounds of the invention are generally at least about 10 times more selective for the D_4 receptor than the D_2 receptor. Preferably, these compounds are at least 20, and more preferably at least 25-50, times more selective for the D_4 receptor than the D_2 receptor. Most preferably, these compounds are at least about 100 times more selective for the D_4 receptor than the D_2 receptor.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood

that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

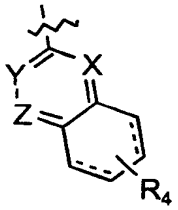
What is claimed is:

1. A compounds of the formula:



or pharmaceutically acceptable addition salts thereof; wherein:

R_a represents

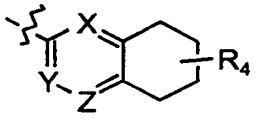


where X, Y and Z are the same or different and represent CH or nitrogen, provided that at least one of X, Y and Z is nitrogen;

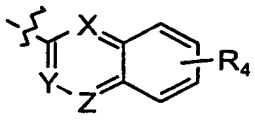
R_1 R_2, R_3 and R_4 independently represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy or SO_2NH_2; and

R_5 is hydrogen, C_1-C_6 alkyl or halogen.

2. A compound according to claim 1, wherein R_a is



3. A compound according to claim 1, wherein R_a is



4. A compound according to claim 2, wherein X is nitrogen and Y and Z are CH.

5. A compound according to claim 2, wherein X and Y are nitrogen and Z is CH.

6. A compound according to claim 2, wherein X and Z are nitrogen and Y is CH.

7. A compound according to claim 3, wherein X is nitrogen and Y and Z are CH.

8. A compound according to claim 3, wherein X and Y are nitrogen and Z is CH.

9. A compound according to claim 3, wherein X and Z are nitrogen and Y is CH.

10. A compound according to claim 4, wherein R_1 and R_2 are hydrogen, C_1-C_6 alkyl, halogen, or hydroxy and R_3 is hydrogen.

11. A compound according to claim 4, wherein R_3 is 4-C_1-C_6 alkyl.

12. A compound according to claim 4, where R_1 and R_2 represent hydrogen, halgogen, C_1-C_6 alkyl, or hydroxy, provided that one of R_1 and R_2 is hydrogen.

13. A compound according to claim 12, where R_5 is C_1-C_6 alkyl.

14. A compound according to claim 6, wherein R_1 and R_2 are hydrogen, C_1-C_6 alkyl, halogen, or hydroxy and R_3 is hydrogen.

15. A compound according to claim 6, wherein R_3 is 4-C_1-C_6 alkyl.

16. A compound according to claim 6, where R_1 and R_2 represent hydrogen, halgogen, C_1-C_6 alkyl, or hydroxy, provided that one of R_1 and R_2 is hydrogen.

17. A compound according to claim 16, where R_5 is C_1-C_6 alkyl.

18. A compound according to claim 7 wherein R_1 and R_2 are hydrogen, C_1-C_6 alkyl, halogen, or hydroxy and R_3 is hydrogen.

19. A compound according to claim 7, wherein R_3 is 4-C_1-C_6 alkyl.

20. A compound according to claim 7, where R_1 and R_2 represent hydrogen, halgogen, C_1-C_6 alkyl, or hydroxy, provided that one of R_1 and R_2 is hydrogen.

21. A compound according to claim 20, where R_5 is C_1-C_6 alkyl.

22. A compound according to claim 8, wherein R_1 and R_2 are hydrogen, C_1-C_6 alkyl, halogen, or hydroxy and R_3 is hydrogen.

23. A compound according to claim 8, wherein R_3 is 4-C_1-C_6 alkyl.

24. A compound according to claim 8, where R_1 and R_2 represent hydrogen, halgogen, C_1-C_6 alkyl, or hydroxy, provided that one of R_1 and R_2 is hydrogen.

25. A compound according to claim 24, where R_5 is C_1-C_6 alkyl.

26. A compound according to claim 1, which is 2-{4-[(2-phenylimidazol-5-yl)methyl]piperazinyl}quinazoline.

27. A compound according to claim 1, which is 2-(4-{2-Phenylimidazol-5-yl}methyl]piperazin-1-yl)-5,6,7,8-tetrahydroquinazoline.

28. A compound according to claim 1, which is 2-(4-[{2-(4-Methylphenyl)imidazol-5-yl}methyl]piperazin-1-yl)-5,6,7,8-tetrahydroquinazoline hydrochloride.

29. A compound according to claim 1, which is 2-(4-[{2-(3-Fluorophenyl)imidazol-5-yl}methyl]piperazin-1-yl)-5,6,7,8-tetrahydroquinazoline hydrochloride.

30. A compound according to claim 1, which is 2-(4-[{2-Phenyl-5-methylimidazol-4-yl}methyl]piperazin-1-yl)-5,6,7,8-tetrahydroquinazoline dimaleate.

31. A compound according to claim 1, which is 1-[(2-phenylimidazol-5-yl)methyl]-4-(2-5,6,7,8-tetrahydroquinolyl)piperazine.

32. A compound according to claim 1, which is (1-[(2-phenylimidazol-5-yl)methyl]-4-(2-5,6,7,8-tetrahydroquinolyl)piperazine hydrobromide.

33. A compound according to claim 1, which is 1-[(2-phenylimidazol-5-yl)methyl]-4-(2-quinolyl)piperazine.

34. A compound according to claim 1, which is 1-[(2-phenylimidazol-5-yl)methyl]-4-(2-quinolyl)piperazine hydrobromide.

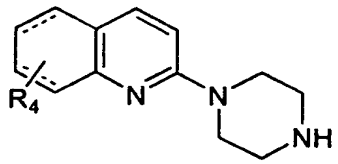
35. A compound according to claim 1, which is 2-(4-[{2-Phenylimidazol-5-yl}methyl]piperazin-1-yl)-6-fluoroquinoline hydrobromide.

36. A compound according to claim 1, which is 1-{[2-(2-fluorophenyl)imidazol-5-yl]methyl}-4-(2-quinolyl)piperazine.

37. A compound according to claim 1, which is 1-{[2-(2-fluorophenyl)imidazol-5-yl]methyl}-4-(2-quinolyl)piperazine oxalate.

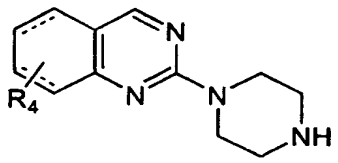
38. A compound according to claim 1, which is 2-{4-[(2-phenylimidazol-5-yl)methyl]piperazinyl}quinoxaline.

39. A compound of the formula:



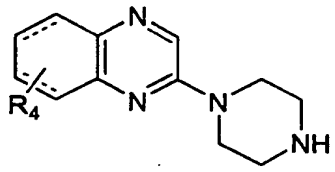
where R_4 represents hydrogen, halogen, hydroxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy or SO_2NH_2.

40. A compound of the formula:



where R_4 represents hydrogen, halogen, hydroxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy or SO_2NH_2.

41. A compound of the formula:



where R_4 represents hydrogen, halogen, hydroxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy or SO_2NH_2.